Factor VIII Inhibitors: An Overview

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- Inhibitors
  - definition, characteristics, frequency of occurrence
- The Problem of Inhibitors from the Regulatory Standpoint
- Inhibitor Risk Assessment
- Workshop Agenda

Factor VIII Inhibitors

- Antibodies to factor VIII may be seen in patients with hemophilia A who receive factor VIII concentrates as therapy or prophylaxis against bleeding.
- Inhibitor antibodies manifest themselves by neutralizing factor VIII activity and/or accelerating the clearance of factor VIII.

Factor VIII Inhibitors

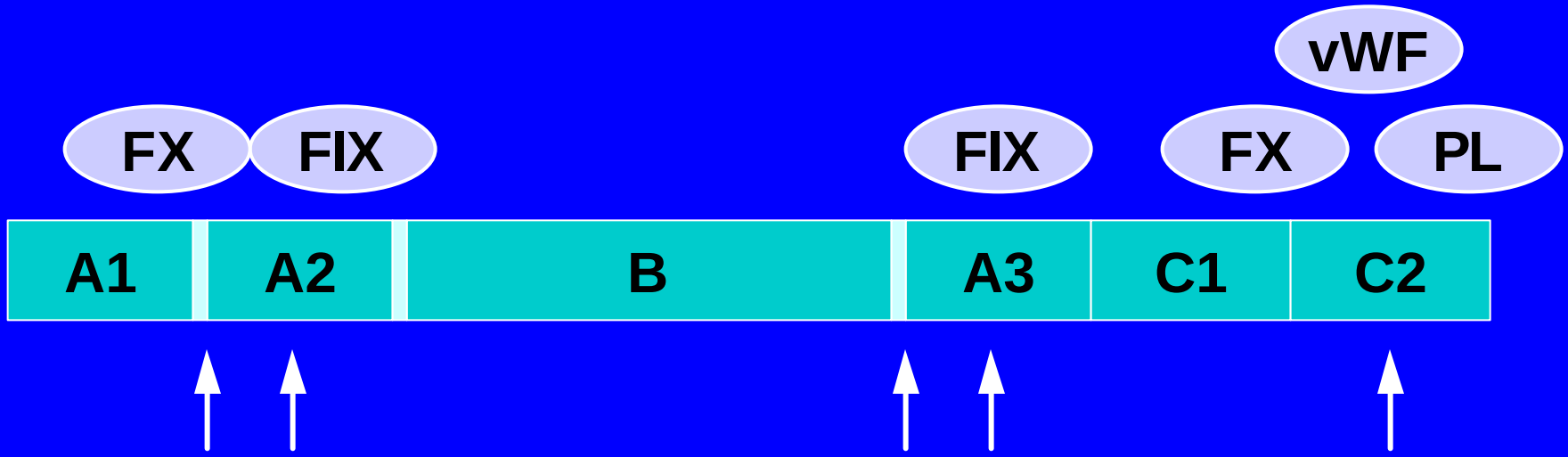
- Inhibitor neutralizing ability is measured *in vitro* by assessing factor VIII activity after incubation with inhibitor plasma.
- Factor VIII falloff studies are *in vivo* tests where elimination of infused factor VIII from the circulation is measured in patients.

Factor VIII Inhibitors

- Complement fixation, immune complex disease, and anaphylaxis are rare, in contrast to factor IX inhibitors.
- Factor VIII inhibitors are typically IgG_4 antibodies with specificity for factor VIII epitopes (Fulcher *et al*, 1987; Hoyer *et al*, 1988).
  - interfere with vWF, PL, F IX, F X binding
  - may catalyze proteolytic cleavage of factor VIII

Factor VIII Inhibitors

- Inhibitor epitopes are clustered in the factor VIII protein
  - (Scandella 2002; Barrow *et al*, 2001).



Factor VIII Inhibitors

- The antibody response to factor VIII is characterized by the titer of the antibody and the nature of the anamnestic response.

- High *vs* low titer; high *vs* low anamnestic response

Factor VIII Inhibitors

- Factor VIII inhibitor incidence depends on patient factors, environmental factors, and sometimes the factor VIII product itself.

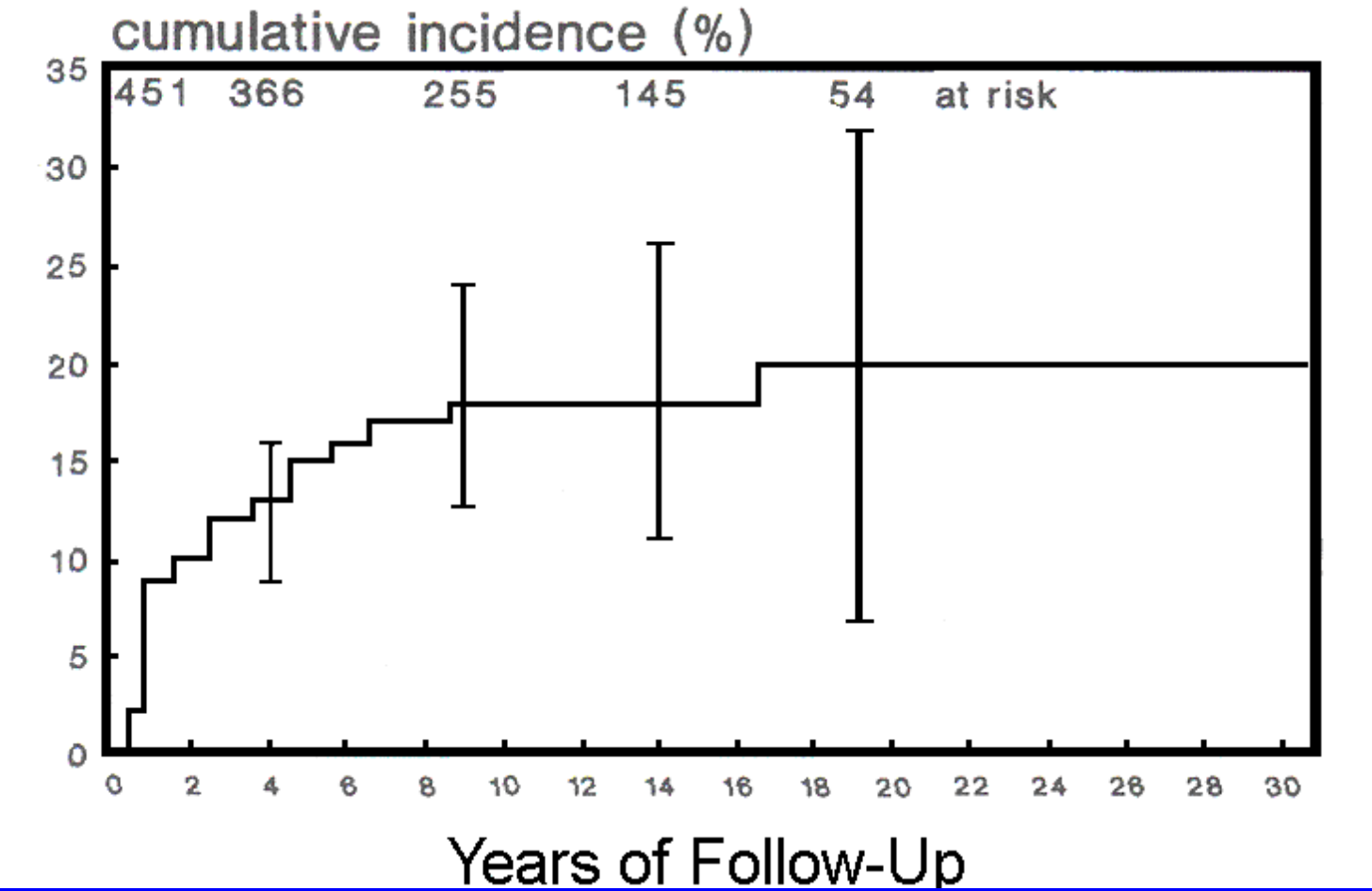
Factor VIII Inhibitors

- The overall rate of factor VIII inhibitor development is on the order of ~20%, though there is great variability in the data.
  - severity of hemophilia
  - frequency of inhibitor assessment
  - threshold for positive inhibitor

Factor VIII Inhibitors

- Greatest inhibitor incidence in those with no prior exposure to factor VIII, the previously untreated patients or “PUPs”.
- Lowest inhibitor incidence in previously treated patients (“PTP’s).

Factor VIII Inhibitors



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Briet, et al., 1994

Patient Factors

- Severity of hemophilia
- Nature of the mutation
  - inversions, deletions, nonsense mutations *vs.* missense mutations, smaller deletions
  - "CRM+" vs. "CRM-" status
- Other genetic factors
  - HLA? race?
  - cytokine/immune response modifier genes?

Environmental Factors

- Co-morbid disease states
  - infection
  - (autoimmune conditions)?
  - pregnancy
  - malignancy
- Concomitant surgery/trauma
- Infusion method, Rx intensity?

Factor VIII Concentrates

- Plasma derived factor VIII (1960's to present)
  - cryoprecipitate (<1 IU/mg)
  - chromatography purified (10-20 IU/mg)
  - monoclonal Ab purification (>2000 IU/mg)
- Recombinant factor VIII (1980's to present)
  - fermentation of factor VIII-transduced cells
  - purification by monoclonal antibodies or other affinity chromatography methods (>2000 IU/mg)

Factor VIII Inhibitors

- Manufacturing process can influence the immunogenicity of factor VIII.

- Seemingly minor changes in virus inactivation procedures associated with outbreak of inhibitors in heavily treated patients.

Dutch Inhibitor Epidemic

- 8 of 140 PTP's with severe hemophilia A developed inhibitors 9 to 45 days after use of a plasma-derived factor VIII concentrate that was solvent-detergent treated and heated at 63º C for 10 hours.
- Titers of 2.2 to 60 Bethesda Units
  - Specificity for the factor VIII light chain
  - Complex inhibition kinetics
- Inhibitors gradually declined when product was stopped.

The Inhibitor Problem

- The problem for FDA and other regulatory agencies is to evaluate new factor VIII products for safety, efficacy, and potency.
- Inhibitor antibodies are the chief adverse event associated with the use of factor VIII since the elimination of HIV and hepatitis viruses.

Inhibitor Risk Assessment

- Definition of inhibitor:
  - what is “positive” and what is “negative”?
  - significance of transient inhibitors?
  - high and low titer definitions?
- Who should participate in trials?
- How should clinical trials be designed?

Inhibitor Risk Assessment

- How should clinical trials be designed?
  - size of trial
  - how many arms
  - appropriate comparator
    - historic controls?
    - compare with current products?
  - role of data safety monitoring board

Inhibitor Risk Assessment

- How do we evaluate clinical trials that assess the inhibitor risk for new factor VIII products?
- Can the regulatory approach be “harmonized” between worldwide regulatory bodies to expedite new product development?

Inhibitor Risk Assessment

- What role should post-marketing surveillance play in regulatory decision-making process?

Workshop Agenda

- Morning sessions will address definition of inhibitors, their laboratory measurement, & clinical epidemiology (US, Canada, UK).
- Afternoon sessions will address design of clinical trials, including FDA and Industry perspectives.
- Conclusion with panel discussion of the issues (Dr. Donna DiMichele).